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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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LOWE HAUPTMAN GILMAN AND BERNER, LLP
1700 DIAGONAL ROAD
SUITE 300 /310
ALEXANDRIA, VA 22314

EXAMINER
MINNIFIELD, NITA M

ART UNIT	PAPER NUMBER
1645	44

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/196,161	Applicant(s) SIN ET AL.	
	Examiner N. M. Minnifield	Art Unit 1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 June 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ they raise the issue of new matter (see Note below);
   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.
   NOTE: _____.
3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a)☒ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *SEE ATTCHED*.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-8*.
   Claim(s) withdrawn from consideration: _____.
8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.
9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *6; 43*.
10. ☐ Other: _____

N. M. Minnifield
Primary Examiner
Art Unit: 1645

ADVISORY ACTION

1. Applicants' After Final Response and 1.132 Declaration filed June 23, 2003 is acknowledged and has been entered.

2. Claims 1-8 are pending in the present application.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1, 3, 4 and 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al (Dev. Biol. Stand. 1997, 90:461). Library of Congress stamped date is August 21, 1997.

The claims are directed to a vaccine comprising a recombinant fusion protein, GST-iAgI, and substantially inert medium (buffer, adjuvant, immunostimulant, or carrier).

Lin et al disclose a recombinant protein, I-antigens as candidates for a recombinant subunit vaccine and indicate that the route of administration may be crucial for the development of a protective antibody response (abstract). Lin et al disclose that "fish surviving infection with the parasitic ciliate *I. multifiliis* are resistant to subsequent challenge suggesting that vaccination is possible." (abstract). Lin et al disclose that "...abundant surface membrane proteins (referred to as immobilization antigens, or I-ags) whose role in eliciting a protective response is indicated by the fact that immune fish produce parasite-immobilizing antibodies in cutaneous mucus and sera..." (abstract). Fish immunized with the i-ag had a survival rate of 25% whereas killed whole cells or crude parasite lysates did not stimulate protective immunity (abstract).

It is noted that the prior art does not specifically recite a substantially inert medium (buffer, adjuvant, immunostimulant, or carrier). However, it would be inherent that a vaccine composition would comprise a buffer, adjuvant or carrier of some kind.

Further, the prior art does not specifically recites recombinant fusion protein; but a recombinant protein is a fusion protein. The prior art anticipates the claimed invention.

Since the Patent Office does not have the facilities for examining and comparing applicants' vaccine with the vaccine of the prior art reference, the burden is upon applicants to show a distinction between the material structural and functional characteristics of the claimed vaccine and the vaccine of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

This rejection is maintained for the reasons of record. Applicant's arguments filed January 31, 2003 have been fully considered but they are not persuasive. Applicants have asserted that the Lin et al reference does not disclose the claimed material, a recombinant fusion protein derived from an artificial DNA sequence for immobilization antigen, repeat I of Ich. Applicants also assert that the art does not relate to the artificial DNA sequences. However, the phrase "derived from an artificial DNA..." is viewed as a process limitation. The prior art discloses the recombinant protein as claimed. Further, as previously stated, a recombinant protein is a fusion protein. The prior art discloses the claimed composition, absent any convincing evidence to the contrary.

The rejection is maintained for the reasons of record. Applicant's arguments filed June 23, 2003 have been fully considered but they are not persuasive. The Sin Declaration under 37 CFR 1.132 filed June 23, 2003 is insufficient to overcome the rejection of claims 1, 3, 4 and 6-8 based upon 102(b) anticipation as set forth in the last Office action.

With regard to Applicants' assertions set forth in the Response of June 23, 2003, Applicants' assertions have been previously addressed. Applicants assert that the most important feature is the material of the vaccine, that is the specific sequence of the claimed fusion protein and that the instant sequence is substantially different from the sequence of the prior art reference(s). However, the pending claims do not specifically recite a specific amino acid sequence or

nucleic acid sequence; no specific SEQ ID NO is recited to define structure to the claimed protein. Applicants have asserted that the instant fusion protein is produced by an artificial DNA sequence and that the difference in the process of making the claimed product is a very important part of characterizing the claimed product. Applicants have asserted that there are 30 differences between the claimed product and the product of the prior art. Applicants have asserted that the instant fusion protein is produced by *E. coli*, which is different from the prior art and suggest that the prior art in general had not published any information on recombinant proteins developed for immobilizing antigens of the protozoan at issue here. Again, the Examiner points out that the claimed invention is a product, and the process by which it is made is irrelevant so long as the properties of the prior art product are the same as that claimed by Applicants. The phrase "derived from an artificial DNA..." is viewed as a process limitation. Further, the term "derived" suggests that modifications or changes are made to the DNA sequence and ultimately the amino acid sequence of the protein. The minor differences shown in the comparison figure could be variants since it appears that the same protein is produced, an immobilization antigen. It would appear that the properties would be the same. Additionally, it is noted that the 102(b) anticipation rejection is based on Lin et al, 1997, not Clark et al, 1992.

With regard to the 1.132 Declaration, declarant believes the material referred to by Lin et al is the same material that has been characterized by Clark et al in their 1992 publication. The Examiner has no way of assessing declarant's position, and it should be noted that the anticipation rejection is based on Lin et al 1997 only. Declarant made a comparison of the sequence listing of the material disclosed in Clark et al with the sequence listing for the material of the instant

claims. Again, the anticipation rejection is based on Lin et al 1997 not Clark et al. Further, it should be noted that no specific nucleic acid sequence is set forth in any of the pending claims in this application. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., nucleic acid sequence or amino acid sequence) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

On page 2 of the declaration declarant refers to Sin et al, 1997 and Clark et al. Declarant asserts that Sin et al 1997 (the claimed material) is 95% effective and Clark et al is only 57% effective in terms of vaccine protection. Declarant asserts that the vaccines are substantially different in structure and act substantially differently. Declarant asserts that Sin et al in Table 1 shows a control with 55% survival whereas "immune" samples of Lin et al have 57% survival. Again, the Examiner notes that the anticipation rejection is based on Lin et al 1997, not Clark et al or Sin et al, 1997. In addition, the claimed invention does not specifically recite any protection levels or percentage of protection the vaccine must possess. The Examiner views the recitation of "vaccine" as a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re*

Casey, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

The lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps, which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." In re Brown, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972)

5. Claims 2 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al (1997) as applied to claims 1, 3, 4 and 6-8 above, and further in view of Clark et al (PNAS, 1992, 89:6363-6367) and Smith et al (Gene, 1998, 67:31-40).

Lin et al teaches a recombinant protein, I-antigens as candidates for a recombinant subunit vaccine and indicate that the route of administration may be crucial for the development of a protective antibody response (abstract). Lin et al teaches that "fish surviving infection with the parasitic ciliate *I. multifiliis* are resistant to subsequent challenge suggesting that vaccination is possible." (abstract). Lin et al teaches that "...abundant surface membrane proteins (referred to as immobilization antigens, or I-ags) whose role in eliciting a protective response is indicated by the fact that immune fish produce parasite-immobilizing antibodies in cutaneous mucus and sera..." (abstract). Fish immunized with the i-

ag had a survival rate of 25% whereas killed whole cells or crude parasite lysates did not stimulate protective immunity (abstract).

It is noted that the prior art does not specifically recite a substantially inert medium (buffer, adjuvant, immunostimulant, or carrier). However, it would be inherent that a vaccine composition would comprise a buffer, adjuvant or carrier of some kind.

Further, the prior art does not specifically recites recombinant fusion protein; but a recombinant protein is a fusion protein.

Lin et al teach the claimed invention except for the specific fusion protein GST-iAg and that the fusion protein is produced in *E. coli.*

However, Clark et al teaches the expression of the immobilization antigen (i.e. i-ag); the cDNA encode a protein of 394 amino acids with a tandemly repeated structure characteristic of the i-antigen of other ciliated parasites (abstract). Clark et al teaches that the immobilization antigens of *I. multifiliis* are analogous to free-living ciliates and parasitic protozoa; and "...that transcript levels increase in parallel with the infectivity of the organism bears on the functional role in this system and is consistent with previous observations suggesting that the i-antigens of *Ich* are involved in the development of protective immunity in fish. (p. 6363, col. 2; see also p. 6367, col. 2). The materials and methods teach how to obtain a recombinant immobilization antigen (p. 6363-6365).

Smith et al teach how to make and purify fusion proteins (foreign protein with GST) that have been produced in *E. coli.* (abstract; p. 38, col. 1). Smith et al teach that expression and purification of parasitic antigens (p. 33, col. 20). Smith et al teach that using GST and *E. coli* provide a better recombinant fusion protein because it avoids the difficulties of denaturing reagents altering the antigenicity and functional activity of the purified product and immunological analysis (p. 32, col. 1).

In view of the combination of references (Lin et al, Clark et al and Smith et al) it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the methods of making recombinant fusion protein (GST-iAgI) using *E. coli* to produce the recombinant fusion proteins with the reasonable expectation of success of making a vaccine comprising a recombinant fusion protein, GST-iAgI, and substantially inert medium. Lin et al teach that the antigen could be a recombinant subunit vaccine. Clark et al teach that other parasitic immobilization antigens are similar and Smith et al suggest and teach making recombinant fusion proteins (GST and a parasitic protein) and that they can be produced in E. coli, the same as Applicants. It would have been obvious to a person of ordinary skill in the art at the time the invention was made at to use

the vaccine of Lin et al comprising the recombinant protein iAgI and adjuvant with a reasonable expectation of protecting against infection of other taxonomically related ciliated protozoan as set forth in Clark et al. Clark et al teach that other taxonomically related ciliated protozoan have the I-antigen (immobilization antigens). The claimed invention is prima facie obvious in view of the prior art absent any convincing evidence to the contrary.

The rejection is maintained for the reasons of record. Applicant's arguments filed January 31, 2003 have been fully considered but they are not persuasive. Applicants have asserted that Clark et al does not disclose artificial DNA sequences or fusion proteins derived therefrom. It is noted that this rejection is a 103 obviousness rejection in view of three references (Lin et al in view of Clark et al and Smith et al). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The prior art in combination as described above teaches the claimed invention. It is noted that Clark et al teaches the DNA and amino acid sequence of the immobilization antigen of Ich. Further, Applicants' claims do not recite the specific DNA sequence. It would appear that the DNA sequence and the artificial DNA sequence would be the same, since both produce recombinant proteins of the immobilization antigen of Ich. Applicants have not shown any evidence that the artificial DNA sequence would produce a better immobilization antigen for a vaccine composition for immunizing fish against ciliated ectoparasitic protozoans or any other superior or unexpected results with regard to the claimed invention.

The rejection is maintained for the reasons of record. Applicant's arguments filed June 23, 2003 have been fully considered but they are not persuasive. Applicants have asserted that the principal reference (Lin et al) discloses a protein sequence that is substantially different (different in 30 distinct particulars) from the fusion protein being claimed and that nothing in the secondary references would suggest these 30 changes to a person of ordinary skill in this art. However, as previously stated the claimed invention does not set forth

a specific sequence (i.e. SEQ ID NO); Lin et al does not specifically disclose a sequence but does teach a composition comprising an immobilization antigen, which is what Applicants have claimed. The references (Lin et al, Clark et al and Smith et al) taken as a whole would suggest the claimed invention to one of ordinary skill in the art at the time the invention was made. With regard to the 30 differences in the sequence, the claims do not recite a specific amino acid or nucleic acid sequence. It is generally known in the art the minor modifications or changes can be made in a sequence (amino acid or nucleic acid) that will result in variants, but not affect the property of the protein.

Again, this rejection is a 103 obviousness rejection in view of three references (Lin et al in view of Clark et al and Smith et al). In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The prior art in combination as described above teaches the claimed invention. It is noted that Clark et al teaches the DNA and amino acid sequence of the immobilization antigen of Ich. Further, Applicants' claims do not recite the specific DNA sequence. It would appear that the DNA sequence and the artificial DNA sequence would be the same, since both produce recombinant proteins of the immobilization antigen of Ich. Applicants have not shown any evidence that the artificial DNA sequence would produce a better immobilization antigen for a vaccine composition for immunizing fish against ciliated ectoparasitic protozoans or any other superior or unexpected results with regard to the claimed invention.

6. No claims are allowed.

7. It is noted that claims that specifically recite the nucleic acid or amino acid sequence (i.e. define by SEQ ID NO) of the immobilization antigen fusion protein would be considered. However, this type of claim would have to searched (sequence search and prior art) and further considerations of enablement under 112, first paragraph.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 703-305-3394. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 703-308-3909. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

NITA MINNIFIELD
PRIMARY EXAMINER
AU 1645
8/5/03